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EXAMINER	
LANDSMAN, ROBERT S	
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1647	23

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/148,012	Applicant(s) KRIEGER, MONTY	
	Examiner Robert Landsman	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 19-22* is/are pending in the application.

4a) Of the above claim(s) *19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 December 1998* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Formal Matters

A. Amendment C, filed 7/17/01, has been entered into the record.

B. The Power of Attorney, filed 4/08/02, has been entered into the record. This Power of Attorney revokes all powers given to previous attorneys and appoints Patrea L. Pabst, Rivka Monheit and Zhaoyang Li to prosecute all transactions and business in the Patent and Trademark Office connected therewith.

C. Amendment D, filed 2/21/02, has been entered into the record.

D. Claims 1-16 were pending in the application and were subject to restriction (Paper No. 19). In Amendment D, the Applicant has amended claim 1 and added new claims 19-22. New claims 19-22 do not contain new matter. However, claim 19 is being withdrawn from consideration as being drawn to a non-elected invention as discussed in the following section entitled "Election/Restriction." Therefore, claims 1-16 and 20-22 are pending and are the subject of this Office Action.

E. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

2. Election/Restriction

A. In the Office Action dated 12/18/01, the pending claims, 1-16, were subject to restriction and were divided into eight Groups. Group I, claims 1-16, in part, drawn to a method of inhibiting SR-BI function, or expression in a mammal using cDNA, or antisense; Group II, claims 1-16, in part, drawn to a method of inhibiting SR-BI function, or expression in a mammal using antibodies; Group III, claims 1-16, in part, drawn to a method of inhibiting SR-BI function, or expression in a mammal using SR-BI binding small molecules; Group IV, claims 1-16, in part, drawn to a method of inhibiting SR-BI function, or expression in a mammal using proteins; Group V, claims 1-16, in part, drawn to a method of increasing SR-BI expression in a mammal using cDNA, or antisense; Group VI, claims 1-16, in part, drawn to a method of increasing SR-BI expression in a mammal using antibodies; Group VII, claims 1-16, in part, drawn to a method of increasing SR-BI expression in a mammal using SR-BI binding small molecules; and Group VIII, claims 1-16, in part, drawn to a method of increasing SR-BI expression in a mammal using proteins.

However, in the response to this restriction requirement, dated 2/21/02, the Applicant argues that unity of invention exists where compounds included within a Markush Group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility. The Applicant argues that all members of the claimed Markush Group share a common mechanism of action, i.e. binding to either the gene encoding SR-BI, or the SR-BI protein itself. First, the Examiner points out that, while all of these compounds in the Group may share a common utility, they do not, in fact, share a substantial structural feature (i.e. common core). cDNA and antisense nucleic acid molecules, for example, have a different structure than antibodies which, themselves, have a different physical structure than small molecules and binding proteins. Furthermore, compounds which bind to a gene encoding a protein act via a different mechanism than compounds which bind to the protein encoded for by that gene. Therefore, the Markush Group which brought about the eight-way restriction requirement is improper. The Applicant states that the claims have been amended to delete the language that gave rise to this restriction requirement. However, new claim 19 recites a method for altering lipoprotein, HDL, LDL, or cholesterol levels in a mammal by administering an antibody to SR-BI, whereas new claim 20 recites a method for altering lipoprotein, HDL, LDL, or cholesterol levels in a mammal by administering a drug that binds SR-BI, which encompasses compounds other than antibodies, such as small molecules. Therefore, claim 20 is being examined only insofar as it reads on small molecules. Applicants further state that, to the extent that the Examiner requires an election of species, they have elected cholesterol-lowering small molecules and, for the disorder, infertility. However, respectfully, the pending claims were subject to a restriction and not an election of species, nor did the restriction requirement include an election of species for a disorder. Therefore, the species election made by the Applicant will be treated as a response to a restriction requirement and claim 19 will not be examined as it is drawn to a non-elected invention. Claims 1-16 and 20-22 will be considered a single invention and are the subject of this Office Action. This restriction is deemed proper and is, therefore, made FINAL.

3. Formal Drawings

A. The Formal Drawings, filed 12/10/98, have been reviewed by the Draftsperson and are accepted by the Examiner.

4. Claim Objections

A Claim 9 is objected to since the syntax can be improved by inserting the word "an" between the word "by" and "overproduction."

B Claim 10 is objected to since the syntax can be improved by inserting the word "an" between the word "by" and "underproduction."

5. Claim Rejections - 35 USC § 112, first paragraph – written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claims 1-16 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1, from which all of these rejected claims ultimately depend, recites a method for altering fertility, or treating a reproductive disorder in a mammal comprising administering a compound which alters lipoprotein, LDL, HDL, or cholesterol levels in the mammal.

These are genus claims. The claims encompass a universe of compounds. However, Applicant has only provided written description of a small number of specific compounds which act via SR-BI, including estrogen (Example 3 on pages 39-40 of the specification), adenoviral vector encoding SR-BI (Example 5 on pages 40-45 of the specification), and anti-SR-BI antibody (Example 8 on pages 55-66 of the specification). However, Applicant has provided no written description of any compounds which alter fertility or treat reproductive disorders by altering lipoprotein, LDL, HDL, or cholesterol levels in the mammal. Applicants have only described that knocking out the SR-BI gene produces sterile (i.e. altered fertility) transgenic female mice (Example 6, pages 45-54 of the specification).

Furthermore, claims 1-7, 15, 16 and 20-22 recite, or read on, altering SR-BI receptors, or affecting receptor binding to lipoproteins, in *any* tissue. Applicant has not provided adequate written description of which specific tissues modulation of SR-BI would be required in order to alter fertility or to treat *any and all* reproductive disorders. Applicant has only demonstrated that completely knocking out the SR-BI gene (i.e. from all tissues) causes female mice to be infertile (Example 6). However, in the other examples in the specification, Applicant does not describe how altering SR-BI levels in these tissues alone affects fertility or reproductive disorders in a mammal, or if altering SR-BI levels *at all* in these tissues is sufficient to alter fertility or treat *any and all* reproductive disorders in a mammal. For example, in Examples 3 and 4, Applicants have only shown that estrogen-treated rats show an upregulation of SR-BI in adrenal membranes (page 39, line 30 – page 40, line 1) and ovaries (page 40, lines 20-23).

Applicants have also demonstrated the effect of hepatic SR-BI overexpression on plasma cholesterol levels (Example 4, especially page 41, lines 12-14 and Table 1). Again, no nexus between SR-BI expression in these tissues and the ability to alter fertility or reproductive disorders has been described.

Additionally, Applicant has not recited the appropriate dosages of any compounds to alter fertility or treat any and any possible reproductive disorders, nor have they described to what extent the lipoprotein, LDL, HDL, or cholesterol levels need to be altered in the mammal to effectively alter fertility or to effectively treat any and all reproductive disorders. There is also no written description as to what length of time these compounds would need to be administered in order to alter fertility or to treat any and all reproductive disorders. Though fertility and reproductive disorders *may* all be affected by lipoprotein, LDL, HDL, or cholesterol levels, they likely all have a different mechanism of action since they are all different conditions and Applicant has not adequately described these conditions (e.g. disorders), nor what level of alteration of lipoprotein, LDL, HDL, or cholesterol levels in a mammal would be required. Finally, Applicant has not described how lipoprotein, LDL, HDL, or cholesterol levels would alter fertility in male mice, since male SR-BI knock out mice were fertile (page 49, lines 21-22). Claims 2-16 and 20-22 are rejected since they depend from rejected claim 1.

6. Claim Rejections - 35 USC § 112, first paragraph – scope of enablement

A. The rejection of claims 1-16 remain rejected under 35 USC 112, first paragraph, and new claims 20-22 are also rejected for the reasons already of record on pages 3-5 of the Office Action dated 4/11/01. The scope of enablement rejection, which was *originally* stated on pages 7-8 of the Office Action dated 9/11/00, recited that while the specification was "enabling for estrogen (Example 3) and SR-BI antibody (Example 8), does not reasonably provide enablement for all compounds listed on page 11, lines 11-17 of the specification." However, upon further review of the specification, as well as the amendment of claim 1 in Paper No. 21, the rejection of claims 1-16 and 20-22 has been broadened. The rejection and Applicant's arguments are addressed below.

Claims 1-16 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for altering fertility in female mice by knocking out the SR-BI gene, does not reasonably provide enablement for any method of altering fertility or treating *any and all* reproductive disorders by altering lipoprotein, LDL, HDL, or cholesterol levels in a mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants argue on pages 3-5 of the Response dated 7/17/01, that the key to the present invention is the evolutionary conservation between mouse and human SR-BI and that this conservation allows for familiar and routine experimentation, via the various assays cited on page 3 of Applicant's response, dated 7/17/01 as routine in the art, to be conducted by one of skill in the art. The Applicant also argues that this evolutionary conservation also allows for careful extrapolation of the results obtained from such experimentation. Applicant further argues that ligands that bind SR-BI have been described and characterized (e.g. AcLDL, LDL, estrogen, HDL and SR-BI antibodies), that the full-length DNA encoding SR-BI is disclosed in the present specification and that the targeted sequence encoding SR-BI defines the complementary nature of the compounds to be designed. Similar arguments are made on pages 4-5 of the Response of Amendment D, filed 2/12/02 where Applicant argues that the data in the application (Examples 3, 5, 6 and 8) demonstrate that multiple compounds can be used to achieve the method of claim 1. They further support their argument by citing Miettinen et al. (J. Clin. Invenst. 108:1717-1722, 2001), who teach that SR-BI knockout mice are infertile and that fertility was restored by inactivating the apoI gene or administering the cholesterol lowering drug, probucol. However, while these results are interesting, the infertility in these mice was induced by genetic manipulation of an embryonic stem cell. There is no evidence of any female reproductive disorder, including in humans, which acts via SR-BI. Applicant has produced a specific genetic alteration in a stem cell to produce this infertility in female mice and have provided no nexus between a method of altering fertility in an SR-BI knockout female mouse and a method of altering fertility or treating a reproductive disorder by altering lipoprotein, LDL, HDL or cholesterol levels in a mammal which is not an SR-BI knockout. Furthermore, the last line of the abstract of Miettinen et al. is speculative in stating that abnormal lipoprotein metabolism may contribute to some form of human infertility. There is no evidence that altering SR-BI levels in a fertile female with normal SR-BI levels and no reproductive disorders will have the desired effect of the claimed method. Finally, as further evidence for the lack of enablement of the present invention for any method of altering fertility or treating a reproductive disorder besides that to restore fertility in infertile SR-BI knockout female mice, that there is no evidence in the art that women taking cholesterol-lowering drugs experience any fertility problems, demonstrating that cholesterol-lowering drugs, which would meet the limitation of claim 1, may not alter fertility.

In considering Applicant's arguments regarding the examples in the specification demonstrating that various compounds bind SR-BI, the Examiner agrees that the specification does disclose various compounds which bind SR-BI, such as estrogen (Example 3 on pages 39-40 of the specification), adenoviral vector encoding SR-BI (Example 5 on pages 40-45 of the specification), and anti-SR-BI

antibody (Example 8 on pages 55-66 of the specification). SR-BI knockout transgenic mice have also been shown to produce sterile female mice (Example 6, pages 45-54 of the specification). However, as stated by the Examiner in the previous paragraph, knocking out the SR-BI gene in an embryonic stem cell does not enable the artisan to alter fertility or to treat a reproductive disorder in a fully formed mammal by administering a compound which alters lipoprotein, LDL, HDL, or cholesterol levels, regardless of whether or not these compounds are acting through SR-BI.

Continuing with Applicant's arguments, they also argue on pages 4 and 5 of the response dated 7/17/01 that the references provided by the Examiner are concerned with problems encountered while trying to assign function to random genomic sequences and that this is completely different than modeling based on structural biochemical and genetic data from the targeted receptor. These arguments have been considered and are deemed persuasive by the Examiner since, in fact, Applicant is not trying to assign function to random genomic sequences, as taught by the cited references. Therefore, part of the rejection is withdrawn and these reference will not being relied upon in the present rejection under 35 USC 112, first paragraph. However, Applicant still has provided no guidance or working examples of compounds which alter fertility, or treat reproductive disorders by altering lipoprotein, LDL, HDL, or cholesterol levels in a mammal other than in knockout infertile female mice, regardless of whether or not these compounds act via SR-BI, nor has the Applicant provided any guidance or working examples of compounds which alter fertility in males, since SR-BI knockout mice were fertile. These issues are addressed in the following paragraphs of this rejection.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

First, the breadth of the claims is excessive. Claim 1, from which all claims in the present application ultimately depend, recites a method for altering fertility, or treating a reproductive disorder in a mammal, comprising administering a compound altering lipoprotein, LDL, HDL, or cholesterol levels in the mammal. However, Applicant has provided no guidance and working examples of any compounds which act via SR-BI to alter fertility other than those in knockout infertile female mice. In fact, in the specification, estrogen (Example 3 on pages 39-40 of the specification), adenoviral vector encoding SR-BI (Example 5 on pages 40-45 of the specification), and anti-SR-BI antibody (Example 8 on pages 55-66 of the specification) have only been shown to affect SR-BI and to alter cholesterol and lipoprotein levels,

but have not been shown to alter fertility or to treat a reproductive disorder in a mammal. The only method of altering fertility in a mammal that has been demonstrated by the present invention is that showing that SR-BI knockout transgenic female mice are infertile (Example 6, pages 45-54 of the specification). However, a method of knocking out a gene in an embryonic stem cell is not comparable to a method of altering fertility or treating a reproductive disorder in a developed mammal. In addition, the specification and claims provide no guidance or working examples of any method of altering fertility in a male, which, according to the specification, are fertile upon knock out of the SR-BI gene (page 49, lines 21-22).

The instant fact pattern is similar to that in *In re Hyatt*, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), wherein a single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification at most disclosed only those means known to the inventors. When claims depend on a recited property, a fact situation comparable to *Hyatt* is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor.

Furthermore, the claims of the present invention recite, or read on, altering SR-BI receptors in *any* tissue. Applicant has provided no guidance or working examples of which specific tissues modulation of SR-BI would be required in order to alter fertility or to treat *any and all* reproductive disorders. Again, Applicant has only demonstrated that completely knocking out the SR-BI gene (i.e. from all tissues) causes female mice to be infertile (Example 6). In Examples 3 and 4, Applicant has only shown that estrogen-treated rats show an upregulation of SR-BI in adrenal membranes (page 39, line 30 – page 40, line 1) and ovaries (page 40, lines 20-23). Applicant has also demonstrated the effect of hepatic SR-BI overexpression on plasma cholesterol levels (Example 4, especially page 41, lines 12-14 and Table 1). However, no nexus between SR-BI expression in these tissues and the ability to alter fertility or reproductive disorders has been made. It would also be unpredictable to one of ordinary skill in the art how to alter fertility or treat *any and all* reproductive disorders simply by altering lipoprotein, HDL, LDL, or cholesterol levels in a mammal, especially since fertility and reproductive disorders all have a separate mechanism of action, and, in the absence of guidance or working examples, the artisan would not be able to predict which of either lipoprotein, HDL, LDL, or cholesterol, to alter, and to what extent and length of time, in order to produce the desired conditions (i.e. alter fertility or treat a reproductive disorder), especially given that each of these conditions has its own etiology and is likely affected differently by lipoprotein, HDL, LDL, or cholesterol than are the other conditions. This unpredictability is further

supported by the fact that Applicant has provided no guidance or working examples of any method of altering fertility or treating a reproductive disorder by administering *any* compound which alters lipoprotein, LDL, HDL, or cholesterol levels, nor has Applicant taught how altering these levels would alter fertility in male mice, since male SR-BI knock out mice were fertile (page 49, lines 21-22).

In summary, the breadth of the claims is excessive regarding a method for altering fertility, or treating any and all reproductive disorders in a mammal comprising administering *any* compound altering lipoprotein, LDL, HDL, or cholesterol levels in the mammal in *any* specific tissue. Applicants have only shown that a complete knockout of the SR-BI gene alters fertility in female mice. There is also a lack of guidance or working examples of any method altering fertility or treating a reproductive disorder in a mammal by altering lipoprotein, HDL, LDL, or cholesterol levels, as well as any methods altering male fertility by altering these levels. These factors, in addition to the lack of predictability of which of either lipoprotein, HDL, LDL, or cholesterol, to alter, and to what extent and length of time, in order to produce the desired conditions (i.e. alter fertility or treat a reproductive disorder), as well as the lack of predictability of how to alter fertility in male mice, lead the Examiner to hold that undue experimentation is necessary to practice the claimed invention. Claims 2-16 and 20-22 are rejected since they depend from rejected claim 1.

7. Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 and 20-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-16 and 20-22 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the recitation of a treatment regimen including the dose of the claimed compound to be administered and the length of time to administer the compound.

B. Claims 2 and 4-7 recites the limitation "the tissue." There is insufficient antecedent basis for this limitation in claim 1, from which these claims ultimately depend.

8. Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

A. Claims 1-16 and 20-22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 5,962,322. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of altering lipoprotein, or cholesterol by administering a compound is the same in both the patent and the present application.

Claim 1 of the present application, from which all other claims from the application ultimately depend, recites a method for altering fertility or treating a reproductive disorder by administering a compound which alters lipoprotein, LDL, HDL, or cholesterol. Claim 1 of the patent, form which all other claims of the patent ultimately depend, recites a method for selectively altering transport of a lipid, cholesterol, lipoprotein, or component thereof into and out of mammalian cells in an amount effective to alter plasma cholesterol comprising administering a composition in an amount effective to alter expression or activity of SR-BI and thus alter the rate of clearance of the protein component of HDL as compared to the cholesterol ester component of the HDL. The only difference in independent claim 1 of the present application and independent claim 1 of the patent is the preamble and desired goal of both of these claims. However, both claim 1 of the application and claim 1 of the patent only recite one method step, which is identical in both cases. This method step is the administration of a compound or composition which alters cholesterol levels. Claim 1 and 8-14 of the present application do not recite that the composition must act by altering SR-BI expression. However, the scope of these claims encompass compounds which affect SR-BI expression as well as SR-BI binding to other compounds (e.g. HDL, cholesterol). Similarly, the method of claim 1 of the patent, and its dependent claims, does not recite altering fertility or treating a reproductive disorder. However, since the only method step in both claim 1

of the application and claim 1 of the patent is the administration of a compound or composition which alters cholesterol levels, the claims of the present application are being included in this double patenting rejection.

Though Rigotti et al. (J. Biol. Chem. 271:33545-33549; page 9 of the IDS filed 4/19/99) is not being used as a reference in this rejection, it is being cited to elucidate the relationship of SR-BI to cholesterol uptake. Rigotti et al. teach that SR-BI binds HDL and can mediate selective uptake of HDL cholesteryl esters in cells and that selective uptake from HDL is a source of cholesterol for steroidogenesis *in vivo* (Abstract). The alteration of SR-BI binding to HDL or other proteins (as claimed in the present application) would inherently be a method of inhibiting cholesterol since a compound binding SR-BI to inhibit HDL would inhibit cholesterol since cholesterol needs to bind HDL in order to be transported by SR-BI. Both the claims of the application and the claims of the patent teach various methods for altering cholesterol, such as altering SR-BI expression alteration of SR-BI binding to lipoproteins and HDL. Therefore, compounds which increase SR-BI expression would be expected to increase SR-BI binding to HDL and lipoprotein and compounds which decrease SR-BI expression would be expected to decrease SR-BI binding to HDL or lipoprotein. Regarding the claims, claims 1-16 are rejected over claims 1-4 of the patent. Claims 1-4, 6, 8, 9, 12-14 and 16 of the application are further rejected over claims 5 and 6 of the patent, whereas claim 15 of the application is only further rejected over claim 6. Claims 1, 3, 6, 8, 9 and 12-14 of the application are further rejected over claim 7 of the patent. Claims 1-3, 5, 7, 8, 10, 11 and 16 of the application are further rejected over claims 8-10 of the patent. Finally, claims 20-22 of the application are rejected over claims 1, 2, 5 and 7 of the patent.

Claims 1 of the application recites a method of altering fertility or treating a reproductive disorder by administering a compound which alters lipoprotein, LDL, HDL or cholesterol. Claims 2, 4, 5, 15 and 16 of the present application, which depend from claim 1, recite a method using a compound which alters lipoprotein or cholesterol levels where the compound alters SR-BI expression (claim 2) by either decreasing (claim 4), increasing (claim 5), or differentially altering (claim 15) SR-BI expression, or increasing SR-BI expression in reproductive tissues and decreasing, or not affecting SR-BI levels in the liver (claim 16). The present specification demonstrates that estrogen meets the limitation of claims 15 and 16 since Examples 3 and 4 show that estrogen-treated rats show an upregulation of SR-BI in adrenal membranes with no effect on the liver (page 39, line 30 – page 40, line 5). Further support for the dual effects of estrogen is also seen in Rigotti et al. (J. Biol. Chem. 271:33545-33549). Rigotti et al. teach that estrogen induces SR-BI expression in steroidogenic cells of the ovary and adrenal gland and reduces SR-

BI expression in the liver (page 33548, right column, first full paragraph). Claim 8 of the application, which depends from claim 1, recites that the mammal is a female and the compound is administered in an amount to inhibit normal reproductive function. Claims 9-14, which ultimately depend from claim 1, recite that the mammal has either an overproduction (claim 9) or underproduction (claim 10) of steroids, or where the disease can be treated by decreasing the production of steroids (claim 12) and wherein the disorder is menopause (claim 11), prostate or breast cancer (claim 13), or endometriosis or fibroid tumors (claim 14). Claims 3, 6 and 7, which depend from claim 1 of the application, recite a method for altering fertility or treating a reproductive disorder by administering a compound which alters lipoprotein, LDL, HDL, or cholesterol wherein the compound alters binding of SR-BI to HDL or other proteins (claim 3) by either decreasing (claim 6), or increasing (claim 7) said binding.

Again, claim 1 of the patent recites a method of selectively altering transport of a lipid, cholesterol, lipoprotein, or component thereof in mammalian cells in an amount effective to alter plasma cholesterol by administering a compound altering the expression or activity of SR-BI. Claims 2-4 of the patent recites that the transport of the lipid, cholesterol, lipoprotein, or component thereof into various tissues, including steroidogenic tissues, is inhibited or stimulated by administering a hormone, including estrogen, which inhibits or stimulates SR-BI expression. Claims 8-10 recite that compound of claim 1 induces expression of SR-BI (claim 8) and can be either a viral vector (claim 9) or an adenoviral vector (claim 10). Claim 3 of the patent, which ultimately depends from claim 1, recites increasing SR-BI expression. Claim 5 of the patent recites a method of altering cholesterol or lipoprotein by administering a compound which inhibits transport of cholesterol by SR-BI. Claim 7 of the patent recites that the compound binds SR-BI and prevents binding of cholesterol or lipoprotein to SR-BI.

The only difference between the claims of the patent and the claims of the application is that the preamble of claim 1 of the application, from which all claims of the application ultimately depend, is the identification a population in which fertility is to be altered, or a reproductive disorder is to be treated whereas the claim 1 of the patent, form which all other claims of the patent ultimately depend, recites a method for selectively altering transport of a lipid, cholesterol, lipoprotein, or component thereof into and out of mammalian cells in an amount effective to alter plasma cholesterol comprising administering a composition in an amount effective to alter expression or activity of SR-BI and thus alter the rate of clearance of the protein component of HDL as compared to the cholesterol ester component of the HDL. However, the instant invention is not patentably distinct from, and is anticipated by, the prior art of record (the patent) because the previously known method step of altering cholesterol, or lipoprotein, which is the only method step in the claims of both the application and patent, is identical regardless of whether the

purpose is to alter fertility or treat a reproductive disorder, as claimed in the application, or to selectively alter transport of cholesterol or lipoprotein, as claimed in the patent (Ex parte Novitski, 26 USPQ 1391). The claims of the present invention do not recite a separate method step which specifically identifies a population in need of such treatment, but simply recite that administering a compound which alters lipoprotein or cholesterol would have the effect of altering fertility or treating a reproductive disorder. Therefore, the artisan, in performing the methods of the patent, would have had a reasonable expectation of success of altering fertility or treating a reproductive disorder as recited in the application since the methods of the patent would inherently be performing the methods of the application.

9. Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

A. Claims 1-7, 15 and 16 remain rejected under 35 USC 102(a) as being anticipated by Rigotti et al. (Current Opinion in Lipidology 8:181-188, 1997) for the reasons already of record on pages 2-3 of the Office Action dated 4/11/01. Applicant argues that estrogen is associated with a number of side effects (i.e. does not selectively affect SR-BI) and treatment is more preferably achieved through other agents. Applicant argues that estrogen produces many of its effects through up-regulation of LDL receptor expression and that steroids typically bind and activate target receptors in the nucleus to cause gene transcription. However, claim 1, as amended, does not recite that the compounds have to "selectively" increases SR-BI expression. Therefore, administering estrogen meets the limitation of the present claims

(Ex parte Novitski, 26 USPQ 1391). Therefore, respectfully, these arguments are moot and the rejection stands.

B. Claims 1, 2, 4, 5, 15 and 16 are rejected under 35 U.S.C. 102(a) as being anticipated by Rigotti et al. (J. Biol. Chem. 271:33545-33549; page 9 of the IDS filed 4/19/99). Claim 1 recites a method for altering fertility or treating a reproductive disorder in a mammal by providing a compound which alters lipoprotein, LDL, HDL, or cholesterol levels in a mammal. Claims 2, 4, 5 and 15 recite a method for altering fertility or treating a reproductive disorder in a mammal by providing a compound which alters SR-BI expression in the tissue, either by increasing expression, decreasing expression, or differentially altering the expression of SR-BI in different tissues. Claim 16 recites that the compound increases SR-BI expression in reproductive tissues and decreases, or does not increase, SR-BI expression in the liver.

Rigotti et al. teach that SR-BI binds HDL and can mediate selective uptake of HDL cholesteryl esters in cells, and that selective uptake from HDL is a source of cholesterol for steroidogenesis *in vivo* (Abstract). Therefore, the administration of estrogen to rats by Rigotti et al. would meet the limitations of claim 1 of the present invention since Rigotti et al. have shown that estrogen increases SR-BI in the ovary and adrenal glands and that, since Rigotti et al. have taught that SR-BI binds HDL, and HDL would provide a source of cholesterol for steroidogenesis *in vivo*, then an increase in SR-BI expression in cells would then allow the uptake of cholesterol into cells via HDL and its conversion to steroids. This conversion of cholesterol to steroids would inherently alter the level of cholesterol in a mammal since cholesterol would have to be catabolized to produce steroids. Therefore, since Rigotti et al. are altering cholesterol levels in a mammal, this would inherently alter fertility or treat a reproductive disorder in a mammal since the alteration of lipoprotein, LDL, HDL or cholesterol is the only requirement recited in claim 1 in order to perform the claimed method (Ex parte Novitski, 26 USPQ 1391). Rigotti et al. also meet the limitations of claims 2, 5, 15 and 16 since they teach that estrogen induces SR-BI expression in steroidogenic cells of the ovary and adrenal gland, and meet the limitation of claims 2, 4, 15 and 16, since they teach that estrogen reduces SR-BI expression in the liver (page 33548, right column, first full paragraph).

C. Claims 1, 2, 4, 5, 8, 15 and 16 are rejected under 35 U.S.C. 102(a) as being unpatentable by Spona et al. (see Form PTO-892 of Paper 7). Claim 1 recites a method for altering fertility or treating a reproductive disorder in a mammal by providing a compound which alters lipoprotein, LDL, HDL, or cholesterol levels in a mammal. Claims 2, 4, 5 and 15 recite a method for altering fertility or treating a

reproductive disorder in a mammal by providing a compound which alters SR-BI expression in the tissue, either by increasing expression, decreasing expression, or differentially altering the expression of SR-BI in different tissues. Claim 16 recites that the compound increases SR-BI expression in reproductive tissues and decreases, or does not increase, SR-BI expression in the liver. Claim 8 is drawn to the method of claim 1 wherein the compound is being administered to a female in an amount effective to prevent normal reproductive function.

Spona et al. teach the administration of the estrogen, ethinylestradiol (page 299, right column, last paragraph; page 300, "Materials and Methods" under "Study Design") to females who had normal ovulatory cycles (page 300, "Materials and Methods" under "Volunteers") and that this administration inhibited ovulation (page 303, Discussion, first paragraph), thereby preventing normal reproductive function, as recited in claims 1 and 8.

Though Rigotti et al. (J. Biol. Chem. 271:33545-33549; page 9 of the IDS filed 4/19/99) is not being used as a reference in this rejection, it is being cited, as discussed in the above rejection under 35 USC 102(a), only to support the finding that the administration of estrogen meets the limitation of claims 2, 4, 5, 15 and 16. Briefly, Rigotti et al. teach that SR-BI binds HDL and can mediate selective uptake of HDL cholesteryl esters in cells and that selective uptake from HDL is a source of cholesterol for steroidogenesis *in vivo* (Abstract). Therefore, the administration of estrogen to rats by Rigotti et al. would meet the limitations of claim 1 since Rigotti et al. have shown that estrogen increases SR-BI in the ovary and adrenal glands and that this increase in SR-BI expression would increase the uptake of cholesterol in cells via HDL. Rigotti et al. also meet the limitations of claims 2, 5, 15 and 16 since they teach that estrogen induces SR-BI expression in steroidogenic cells of the ovary and adrenal gland, and that the limitation of claims 2, 4, 15 and 16, since they teach that estrogen reduces SR-BI expression in the liver (page 33548, right column, first full paragraph). Therefore, based on the teachings of Rigotti et al. regarding estrogen, Spona et al., who also use estrogen, meet the limitations of claims 1, 2, 4, 5, 8, 15 and 16 (also Ex parte Novitski, 26 USPQ 1391).

D. Claims 1, 2, 4, 5, 9, 12, 13 and 15 are rejected under 35 U.S.C. 102(b) as being unpatentable by Bajetta et. al. (on the Form PTO-892 of Paper No. 7). Claim 1 recites a method for altering fertility or treating a reproductive disorder in a mammal by providing a compound which alters lipoprotein, LDL, HDL, or cholesterol levels in a mammal. Claims 2, 4, 5 and 15 recite a method for altering fertility or treating a reproductive disorder in a mammal by providing a compound which alters SR-BI expression in the tissue, either by increasing expression, decreasing expression, or differentially altering the expression

of SR-BI in different tissues. Claims 9, 12 and 13 are directed to the method of claim 1 where the disorder is characterized by an overproduction of steroids, wherein this disorder can be treated by decreasing the overproduction of steroids, and where the disorder is breast cancer.

Bajetta et. al. teach that formestane, is a selective inhibitor of aromatase, which is responsible for estrogen synthesis (Abstract). They also teach that administration of formestane to women with breast cancer significantly reduced plasma estrogen levels (Abstract). Finally, they teach a significant remission in breast cancer by treatment with two different doses of formestane (page 147, right column, first paragraph and Table II); therefore showing that breast cancer is associated with an overproduction of estrogen and can be treated by decreasing the overproduction of steroids (i.e. estrogen); therefore, meeting the limitation of claim 1, 9, 12 and 13.

Though Rigotti et al. (J. Biol. Chem. 271:33545-33549; page 9 of the IDS filed 4/19/99) is not being used as a reference in this rejection, it is being cited only demonstrate estrogen can increase as well as decrease SR-BI expression, which would then alter cholesterol levels due to an increase or decrease in SR-BI expression. The teachings of Rigotti are cited in the above rejection (Paragraph A) under 35 USC 102(a). Since formestane has been shown to decrease plasma estrogen levels, this compound (formestane), taking into account the teachings of Rigotti et al., would inherently be altering cholesterol levels in the subjects of Bajetta et al., as recited in claim 1, since cholesterol is required for estrogen synthesis. Furthermore, biological organisms utilize numerous feedback and regulatory mechanisms. Therefore, considering the teachings of Rigotti et al. who state that estrogen induces SR-BI expression in steroidogenic cells of the ovary and adrenal gland and reduces SR-BI expression in the liver, it is expected and, in fact, inherent in absence of evidence to the contrary, that if an *increase* in estrogen levels both increases and decreases SR-BI expression in various tissues, then a *decrease* in estrogen levels, as taught by Bajetta et al., would produce the opposite effects on SR-BI expression in the same tissues; therefore, still meeting the limitations of claims 2, 4, 5 and 15 (Ex parte Novitski, 26 USPQ 1391).

E. Claims 1, 2, 4, 5, 9, 12, 14 and 15 are rejected under 35 U.S.C. 102(b) as being unpatentable by Cirkel (on the Form PTO-892 of Paper No. 7). Claim 1 recites a method for altering fertility or treating a reproductive disorder in a mammal by providing a compound which alters lipoprotein, LDL, HDL, or cholesterol levels in a mammal. Claims 2, 4, 5 and 15 recite a method for altering fertility or treating a reproductive disorder in a mammal by providing a compound which alters SR-BI expression in the tissue, either by increasing expression, decreasing expression, or differentially altering the expression of SR-BI in different tissues. Claims 9, 12 and 14 are directed to the method of claim 1 where the disorder is

characterized by an overproduction of steroids, wherein this disorder can be treated by decreasing the overproduction of steroids, and where the disorder is endometriosis.

Cirkel teaches that continuous application of progestogens to treat endometriosis will lead to a hypo-estrogenic endocrine environment causing initial decidualization of endometrial tissues with eventual atrophy (see page 92 under "Progestogens and endometriosis" and Table 3). Therefore, this overproduction of estrogen steroids in endometriosis can be treated by decreasing the production of steroids (i.e. estrogen); therefore, meeting the limitations of claims 1, 9, 12 and 14.

Though Rigotti et al. (J. Biol. Chem. 271:33545-33549; page 9 of the IDS filed 4/19/99) is not being used as a reference in this rejection, it is being cited only demonstrate estrogen can increase as well as decrease SR-BI expression which would then alter cholesterol levels due to increased or decreased SR-BI expression. The teachings of Rigotti are cited in the above rejection (Paragraph A) under 35 USC 102(a). Since progestogens have been shown to decrease estrogen levels, these compounds, taking into account the teachings of Rigotti et al., would inherently be altering cholesterol levels in the subjects of Cirkel, as recited in claim 1. Furthermore, biological organisms utilize numerous feedback and regulatory mechanisms. Therefore, considering the teachings of Rigotti et al. which state that estrogen induces SR-BI expression in steroidogenic cells of the ovary and adrenal gland and reduces SR-BI expression in the liver, it is expected and, in fact inherent in absence of evidence to the contrary, that if an *increase* in estrogen levels both increases and decreases SR-BI expression in various tissues, then a *decrease* in estrogen levels, as taught by Cirkel, would produce the opposite effects on SR-BI expression in the same tissues; therefore, still meeting the limitations of claims 2, 4, 5 and 15 (Ex parte Novitski, 26 USPQ 1391).

F. Claims 1, 2, 4, 5, 10, 11, 15 and 16 are rejected under 35 U.S.C. 102(b) as being unpatentable by Whitcroft et al. (on the Form PTO-892 of Paper No. 7). Claim 1 recites a method for altering fertility or treating a reproductive disorder in a mammal by providing a compound which alters lipoprotein, LDL, HDL, or cholesterol levels in a mammal. Claims 2, 4, 5 and 15 recite a method for altering fertility or treating a reproductive disorder in a mammal by providing a compound which alters SR-BI expression in the tissue, either by increasing expression, decreasing expression, or differentially altering the expression of SR-BI in different tissues. Claim 16 recites that the compound increases SR-BI expression in reproductive tissues and decreases, or does not increase, SR-BI expression in the liver. Claims 10 and 11 are drawn to the method of claim 1 wherein the disorder is an underproduction of steroids, such as menopause.

Whitcroft et al. teach hormone replacement therapy in which the administration of estrogen to menopausal women is used to prevent the long-term consequences of estrogen deficiency (see Abstract and page 15, second column, final full paragraph). This increase in the underproduction of steroids in menopause meets the limitations of claims 1, 10 and 11.

Though Rigotti et al. (J. Biol. Chem. 271:33545-33549; page 9 of the IDS filed 4/19/99) is not being used as a reference in this rejection (cited in the above rejection, Paragraph A, under 35 USC 102(a)), it is being cited only to restate that the administration of estrogen meets the limitation of claims 1, 2, 4, 5 and 15 since estrogen can increase as well as decrease SR-BI expression which would then alter cholesterol levels due to increased or decreased SR-BI expression. Therefore, based on the teachings of Rigotti et al. regarding estrogen, Whitcroft et al., who also use estrogen, meet the limitations of claims 2, 4, 5, 10, 11, 15 and 16 (Ex parte Novitski, 26 USPQ 1391).

G. Claim 1 is rejected under 35 U.S.C. 102(e) as being unpatentable by Reich (U.S. Patent No. 5,674,488). The claim recites a method of altering fertility or treating a reproductive disorder in a mammal by administering compound which alters lipoprotein, LDL, HDL or cholesterol levels in the mammal. Reich teaches a method for lowering blood cholesterol levels in a human by administering an effective amount of a delta 5 hydrogenating enzyme (Abstract, claims 1-6 and 9).

The only difference between the method recited in claim 1 of the present application and the method recited in the Abstract and claim 1-6 and 9 of the patent is the population. The method of the application is drawn toward altering fertility and treating reproductive disorders in a mammal whereas the method of the patent is to treat humans with hypercholesterolemia. However, both claim 1 of the application and the Abstract and claims 1-6 and 9 of the patent only recite one method step, which is identical in both cases. This method step is the administration of a compound or composition which alters cholesterol levels. However, the instant invention is anticipated by, the prior art of record (the patent) because the previously known method step of altering cholesterol, or lipoprotein, which is the only method step in the claims of both the application and patent, is identical regardless of whether the purpose is to alter fertility or treat a reproductive disorder, as claimed in the application, or to lower cholesterol in hypercholesterolemic patients, as claimed in the patent (Ex parte Novitski, 26 USPQ 1391). Claims 2-16 and 20-22 are objected to since they depend from rejected claim 1, but the limitations of these claims is not met by the reference since no nexus could be made between delta 5 hydrogenating enzymes and SR-BI.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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